

Case Report

Early Onset, But Late Diagnosis of a Rare Disease

Pamela Farah, MD^{1*}; Pascale Daniel, MD¹; Georges El Khoury, MD²; Rami El Rachkidi, MD²; Aline Tohme, MD¹

¹Department of Internal Medicine and Clinical Immunology, University Hospital Center Hotel-Dieu de France, Affiliated to Saint-Joseph University, Beirut, Lebanon

²Department of Orthopedic Surgery, University Hospital Center Hotel-Dieu de France, Affiliated to Saint-Joseph University, Beirut, Lebanon

*Corresponding author

Pamela Farah, MD

Faculty of Medicine, Department of Internal Medicine and Clinical Immunology, University Hospital Center Hotel-Dieu de France, Affiliated to Saint-Joseph University, Beirut, Lebanon; E-mail: pamela.farah.26@gmail.com

Article information

Received: May 17th, 2019; Revised: July 9th, 2019; Accepted: July 12th, 2019; Published: July 17th, 2019

Cite this article

Farah P, Daniel P, El Khoury G, El Rachkidi R, Tohme A. Early onset, but late diagnosis of a rare disease. *Intern Med Open J.* 2019; 3(1): 1-3. doi: [10.17140/IMOJ-3-108](https://doi.org/10.17140/IMOJ-3-108)

ABSTRACT

One of the most common sphingolipidosis, Gaucher disease (GD) remains rare till date. A case report of a 56-year-old patient diagnosed with GD is presented herein. Her sister was known to have Gaucher disease. Her personal medical record consisted of splenectomy, anemia, recurrent infections, and bone lesions at a young age. Taking into consideration her personal and familial history, the clinical and paraclinical examinations, she was diagnosed with Gaucher disease which was confirmed with enzyme and gene testing. Upon introduction of specific enzyme replacement treatment for Gaucher patients, much evidence demonstrated the substantial improvement of hematological and visceral parameters. However, it has been observed that the bone tissue does not respond equally to the treatment.

Learning Points

- The physician should always investigate the splenomegaly of unknown etiology before deciding to do a splenectomy
- Bone lesions in Gaucher disease are sometimes irreversible, hence the importance of early diagnosis of this rare disease

Keywords

Gaucher disease; Bone lesion; Splenomegaly.

Acronyms

GD: Gaucher disease; Hb: Hemoglobin; MRI: Magnetic resonance imaging; ERT: Enzyme replacement therapy.

INTRODUCTION

Lysosomal diseases are a group of rare afflictions linked to innate errors of metabolism. Lysosomes are subcellular organelles limited by a membrane and contain many digestive enzymes involved in the catabolism of complex molecules, such as glycolipids, glycoproteins and mucopolysaccharides. The deficiency of a lysosomal enzyme obstructs the degradation of these molecules, causes their accumulation in lysosomes and creates metabolic abnormalities disrupting cell function. There are about fifty lysosomal diseases. Gaucher disease (GD) is one of the most frequent lysosomal diseases,¹ with an incidence of around 1/40,000 to 1/60,000 births in the general population. The disease was first described by Philippe Gaucher in 1882 in a patient with massive splenomegaly

without leukemia. Gaucher is a genetic disease caused by mutations in the *GBA1* gene, located on chromosome 1 (1q21). More than 300 GBA mutations have been described in the *GBA1* gene, and the most common ones are *N370S*, *L444P*, *84GG*, *IVS2*.² The clinical aspects of the disease are caused by a deficiency of the lysosomal enzyme, glucocerebrosidase that leads to the accumulation of its substrate (glucosylceramide) in lysosomal macrophages in the bone marrow, liver, spleen, lungs, and other organs, which contributes to pancytopenia, massive hepatosplenomegaly, and, at times, diffuse infiltrative pulmonary disease. Progressive infiltration of Gaucher cells in the bone marrow may lead to thinning of the cortex, pathologic fractures, bone pain, bony infarcts, and osteopenia. These bony features may also be related to macrophage-produced cytokines. Gaucher disease has traditionally been divided

into the following 3 clinical subtypes:

- Type 1–Non neuronopathic form, which is the most common type
- Type 2–Acute neuronopathic form
- Type 3–Chronic neuronopathic form

However, these distinctions are not absolute, and GD represents a phenotypic continuum.²

A case report of a 56-year-old patient diagnosed with GD is presented herein.

CASE DESCRIPTION

The patient was born from non Jewish consanguineous parents in 1962. She presented to the emergency department in August 2018, for extreme pain on her right hip. The pain was local without specific irradiation, increased on mobilization and improved upon taking rest. It had started one month ago, without trauma or other identified cause, and was not relieved with analgesics.

Her medical record consisted of splenectomy at the age of 9-years-old. Secondary to splenomegaly, recurrent infections in the upper respiratory system, recurrent tonsillitis, anemia that attributed to gynecological loss, fracture at L2 treated with percutaneous cementoplasty in 2014 and an aggressive spinal hemangioma prior to that. Her sister was diagnosed with Gaucher disease at the age of 10-years-old, and she died from the disease's complications at the age of 45.



Figure 1. Erlenmeyer Flask Sign of the Femur

Upon admission, the blood test reports revealed the following results: Hb 11.5 g/dL, MCV 95 fl, white blood cells 8200/mm³, platelets 261000/mm³, ferritin 2654 ng/mL, normal liver function tests, and normal creatinine clearance. Right femoral X-ray revealed an Erlenmeyer flask sign (Figure 1). The magnetic resonance imaging (MRI) of the right hip revealed diffused significant heterogeneity in the signal of the trabecular bone of pelvic bones, femur and the visualized part of the lumbar spine, with

individualization in particular of a much more diffuse and more intense signal abnormality in the spongy bone of the right iliac bone involving the acetabulum and the ilio and ischio-pubic branches, with cortical thinning visible at the height of the iliac crest, and a very important edema of the adjacent soft parts, involving the muscles iliopsoas, glutes, adductors and external obturators on the right side (Figure 2). The MRI concluded no osteonecrosis of the iliac bone, acetabulum and the femoral head.



Figure 2. Diffuse Significant Heterogeneity in the Signal of the Trabecular Bone of Pelvic Bones, Femur

Taking into consideration the clinical presentation of the patient (splenomegaly, hepatomegaly confirmed by abdominal ultrasound, anemia, high ferritinemia, bone lesions) and the family history, the patient was suspected to have Gaucher disease.

In order to confirm the diagnosis, the dosage of the lysosomal enzymes from dried blood, and the molecular genetic testing were performed. The first test revealed that the activity of beta-glucosidase was below its reference range (24.06 pmol/spot*20 h), with an elevated concentration of glucosylsphingosine, and the later tests showed a homozygous mutation of p.V414G which is similar to the known missense mutation p.V414.

The patient was operated in January 2019 with a total right hip replacement and was treated, since November 2018, with intra-venous Imiglucerase (60 UI per kilogram) once every 2-weeks. Moreover, she presented two fractures on D11 and D12, confirmed with lumbar MRI, in March 2019.

DISCUSSION AND CONCLUSION

Although it is the most common all the lysosomal storage diseases, Gaucher disease still remains rare and most cases present a gradual onset phenotype, which explains its delayed diagnosis. The spectrum of the disease is wide, and its clinical manifestation varies from being asymptomatic to presented with all complica-

tions. This patient had presented splenomegaly at infancy, which led to splenectomy at the age of nine, without any diagnosis. It is important to include Gaucher disease in the diagnostic decision tree in cases of splenomegaly and/or thrombocytopenia, in order to avoid potentially harmful splenectomy. Before the advent of enzyme replacement therapy (ERT), total or partial splenectomy was the standard of care for massive splenomegaly or severe pancytopenia.³

Another common manifestation of GD is a bone disease. The bone lesions in Gaucher disease are caused mainly due to alterations in its metabolism (turnover, remodeling, and mineralization), leading to various skeletal complications such as osteoporosis, marrow infiltration, avascular necrosis or osteolysis.⁴ Patients with preexistent skeletal complications tend to suffer episodes during ERT, such as medullary infarctions, avascular necrosis, or fractures, but the frequency of these occurrences is reduced.³ In our case, the patient had aseptic necrosis of the right femoral head and iliac bone that was treated surgically with total hip replacement shortly after being started on ERT.

The efficacy of ERT on hematological and visceral parameters, such as anemia, thrombocytopenia and splenomegaly, is well established in the literature.⁵ However, enzyme therapy cannot reverse established osseous injury; pathological damage such as osteonecrosis, bone infarcts and fracture, once it has occurred, is irreversible. Thereby, despite the low risk of early failure due to aseptic loosening, total hip replacement in patients with Gaucher's disease with symptomatic osteonecrosis of the femoral head is advised.⁴

On an additional matter, patients with GD suffer from early osteopenia. The bone mineral density tends to increase during ERT but with a slow rate, hence early diagnosis and treatment becomes important, in order to avoid severe complications. Fur-

thermore, the use of bisphosphonates can be an effective and safe mean to increase bone density.

CONSENT

The authors have received written informed consent from the patient.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Stirnemann J, Belmatoug N, Camou F, et al. A review of Gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci.* 2017; 18(2): pii: E441. doi: [10.3390/ijms18020441](https://doi.org/10.3390/ijms18020441)
2. Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. *Lancet Neurol.* 2012; 11(11): 986-998. doi: [10.1016/S1474-4422\(12\)70190-4](https://doi.org/10.1016/S1474-4422(12)70190-4)
3. Zimran A. How i treat Gaucher disease. *Blood.* 2011; 118(6): 1463-1471. doi: [10.1182/blood-2011-04-308890](https://doi.org/10.1182/blood-2011-04-308890)
4. Mucci JM, Rozenfeld P. Pathogenesis of bone alterations in Gaucher disease: The role of immune system. *J Immunol Res.* 2015; 2015: 192761. doi: [10.1155/2015/192761](https://doi.org/10.1155/2015/192761)
5. Weinreb NJ, Goldblatt J, Villalobos J, et al. Long-term clinical outcomes in type 1 Gaucher disease following 10 years of imiglucerase treatment. *J Inherit Metab Dis.* 2013; 36(3): 543-553. doi: [10.1007/s10545-012-9528-4](https://doi.org/10.1007/s10545-012-9528-4)